American Journal of Medical Genetics 64:50–58 (1996)

X-Linked Mental Retardation With Thin Habitus, Osteoporosis, and Kyphoscoliosis: Linkage to Xp21.3–p22.12

J. Fernando Arena, Charles Schwartz, Lisbeth Ouzts, Roger Stevenson, Marvin Miller, Judith Garza, Martha Nance, and Herbert Lubs

Department of Pediatrics, University of Miami School of Medicine, Miami, Florida (J.F.A., H.L.); Greenwood Genetic Center, Greenwood, South Carolina (C.S., L.O., R.S.); Department of Pediatrics, Wright State University School of Medicine, Dayton, Ohio (M.M.); Department of Veterans Affairs Medical Center, Minneapolis, Minnesota (M.N.); Department of Medical Genetics, University of Tromsoe, Tromsoe, Norway (H.L.); Department of Pediatrics, University of Rochester, Rochester, New York (J.G.)

We reevaluated a family previously described as having nonspecific X-linked mental retardation (XLMR) by Snyder and Robinson [1969: Clin Pediatr 8:669–674] (MIM 309583). Clinical and DNA studies were conducted on 17 relatives, including 6 males with mild-to-moderate mental retardation, 3 carrier females, and 8 normal males. In contrast to the normal appearance and minimal clinical findings reported 22 years ago, affected males were found to have a characteristic set of clinical findings. These developed gradually over the first 2 decades, and included thin body build with diminished muscle mass, osteoporosis and kyphoscoliosis, slight facial asymmetry with a prominent lower lip, nasal speech, high narrow or cleft palate, and long great toes. Carrier females were clinically normal. Multipoint linkage analysis indicated linkage to markers distal to the 3′ end of DMD (DXS41 and DXS989), with a maximal lod score of 4.7. On the basis of these findings, this entity is redefined as XLMR syndrome.

KEY WORDS: mental retardation, X-linked, XLMR syndrome, Xp21

INTRODUCTION

X-linked mental retardation (XLMR) is considered the most common inherited cause of mental retardation in males. Although recent attention was focused on fragile X syndrome, 60–70% of XLMR cases are caused by other X-linked disorders. One hundred and five XLMR disorders, of which approximately half have been localized or cloned, were listed in a review in the present issue by Lubs et al. [1996a].

The present family (Fig. 1) was reevaluated as part of an ongoing study [Lubs et al., 1996b] to provide more precise clinical descriptions of XLMR, and to localize and identify the responsible genes. The changes in clinical findings from a nonspecific clinical picture in 1969 [Snyder and Robinson, 1969] to a relatively consistent set of clinical abnormalities on reexamination 22 years later illustrate the hazards in classifying a family either as nonspecific or as possessors of a syndrome, and also illustrate the benefits of long-term follow-up and restudy of families with nonspecific XLMR.

MATERIALS AND METHODS

Clinical Studies

The family reported by Snyder and Robinson [1969] was reevaluated by a variety of clinical studies. The pedigree was extended, 5 affected males were reexamined, and one new patient in generation 4, age 2 years, was added (see pedigree, Fig. 1). Other studies included photographs and biometrics of normal and affected relatives. In one case, a muscle biopsy was carried out, and in two cases an MRI was done.

Molecular and Linkage Analysis

Genomic DNA was extracted from blood lymphocytes by standard procedures [Schwartz et al., 1990]. Southern analysis was performed using DNA markers located on the X chromosome [Schwartz et al., 1990]. Probes were labeled by primer extension [Feinberg and Vogelstein, 1983]. Polymorphic $(CA)_n$ repeats were am-

Received for publication August 1, 1995; revision received February 29, 1996.

Address reprint requests to J. Fernando Arena, M.D., Ph.D., Department of Pediatrics, Division of Genetics, Mailman Center for Child Development, University of Miami School of Medicine, P.O. Box 016820 (D820), Miami, FL 33101.

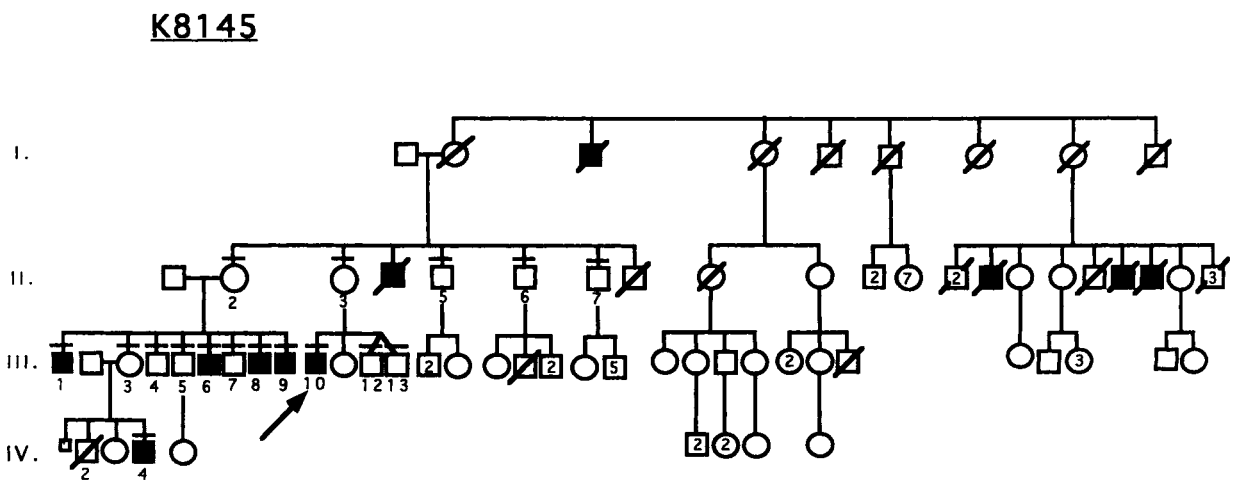

Fig. 1. Pedigree of family K8145, showing pattern of X-linked inheritance. Affected individuals are designated by black squares. Bar over symbol represents family members personally examined.

plified and analyzed according to the conditions specified in Weissenbach et al. [1992]. The glial and muscle promoters for the DMD locus were directly tested using genomic DNA and a set of polymerase chain reaction (PCR) primers based on published sequences [Klamutt et al., 1990; Makover et al., 1991; Gorecki et al., 1992; Rapaport et al., 1992].

Two-point linkage analysis was carried out using MLINK V5.1 [Lathrop and Lalouel, 1984], and multipoint analysis was conducted using LINKMAP V5.1 [Lathrop et al., 1985]. The mutation rate and gene frequency were set at 0.3×10^{-5} and 0.0001, respectively.

Muscle Biopsy

Cryosections of the muscle biopsy on patient III-9 were processed for dystrophin immunofluorescence using the following series of antibodies, listed from the 5′ end: 60 kd polyclonal; 30 kd polyclonal; *Dys*I monoclonal; d10 polyclonal; and d11 polyclonal. Parallel cryosections were stained with H&E and Gomori's modified trichrome to assess the condition of the biopsy and general histopathology.

RESULTS

Clinical Studies: Summary of 1969 Clinical Findings

The principal clinical observations reported in 1969 were normal physical and facial appearance, hypotonia with clumsy movements, and a wide-based gait without clearly abnormal neurological findings. Clinical details were reported on 3 of the 8 affected males (age 4–18 years). Two were noted to have facial asymmetry (ages 38 months and 16 years).

Current Studies

Five affected relatives reported in 1969 as retarded were reexamined. These findings are summarized in Table I, along with observations on a new affected child (IV-4). The present findings in the original index case (III-10) and affected relative III-8, who are representative of the changes occurring in the last 2 decades in the 5 affected adults, are given below. A brief description of IV-4 and his brother (IV-2), who may have died of adrenal insufficiency, is also given. The updated pedigree is shown in Figure 1.

Patient III-10. Patient III-10 (Fig.2) was the index case in the original report. He was born after an uncomplicated pregnancy and delivery. His birth weight was 2,630 g. He walked at 37 months. His height at 38 months was 98 cm (75th centile). He began special education at age 4 years, receiving speech and physical therapy. At age 7 he had seizures and has been on medication ever since. His IQ was 46. He had no other significant medical problems as a child, and his face and habitus were unremarkable. No orbital or facial asymmetry was evident in childhood from a retrospective inspection of photographs (see photograph at age 6 in Fig. 3).

As an adult (age 27 when examined) he lives at home and performs janitorial work, but has never lived independently. He has an asthenic build with diminished muscle bulk and mildly diminished strength (Fig. 2). His thorax is narrow with a slight pectus excavatum. There is also a marked kyphoscoliosis and decreased range of motion at the neck. He has asymmetry of the orbits and slight asymmetry of the lower face (Fig. 3), with a high nasal bridge and a narrow, high-arched palate. He also has long, thin hands (Table I) with long, hyperextensible fingers.

He is oriented to person, place, and time, and is able to read some words. His speech is nasal and dysarthric and not easy to understand. He can follow commands, spell names, and perform simple calculations. His cranial nerve function is normal. His sensory tracts are intact and his reflexes normal. His gait is abnormal due to severe kyphoscoliosis. He was the only affected adult without known osteoporosis or multiple fractures (see Table I), but has not been evaluated for osteoporosis.

Patient III-8. Patient III-8, now a 29-year-old man, was born after an uncomplicated pregnancy and

TABLE I. Clinical Findings*

Clinical findings	Child IV-4	Adults III-1	III-6	III-8	III-9	III-10	Overall (adults)
Age (years)	2	41	32	28	19	27	19–41 years
Height (cm)	82 (5%)	[a]	[a]	187 (95%)	191 (>95%)	[a]	2/2 (tall)
Weight (kg)	9.1 (<5%)	54 (5%)	45 (<5%)	54 (5%)	65 (35%)	42 (<5%)	4/5 (low)
Habitus/skeletal							
Thin, with muscle hypoplasia	−	+	++	++	±	++	5/5
Kyphoscoliosis	−	−	++ (rod)	+	+	+	4/5
Osteoporosis		+	+	+	+		4/4
Pectus excavatum		−	+	−	+	+	3/5
Narrow chest		−	+	+	+	+	4/4
Long hands	− (20%)	+ (>97%)	+ (97%)	+ (>97%)	+ (>97%)	+ (>97%)	5/5
Hyperextensible fingers		−	+	+	+	+	4/5
Long great toes	Hammer toe	Clubfoot	+	+	+	Unknown	
Head							
Asymmetry	Mouth (when crying)	Mouth (slight)	Mouth (slight)	Orbital and mouth	−	Orbital	4/5
Lip disparity[c]	+	+	+	+	+	+	5/5
Palate abnormal		−	Cleft	−	Cleft	High narrow	3/5
Speech		Incomprehensible	Nasal/dysarthric	Thick/slow	Nasal	Nasal/dysarthric	5/5
Neuromuscular							
Abnormality	Involuntary jerks	Spastic paraplegia, incontinent	−		Hypotonia, intention tremor, dysmetria	Seizures	3/5
IQ/retardation	Delayed development	Retarded	70	60	Verbal-86/ Performance-70	46	46–77
Overall status		Unable to sit (in wheelchair)	Works as janitor	Works as janitor	Works in library	Works as janitor	
Other	Testes not descended	Multiple fractures as child Dx of possible osteogenesis imperfecta	Multiple fractures as child Vertebral Fusion of T4-L3 Harrington rod Normal phosphokinase[b]	Thoracic vertebra fractures Colectomy for ulcerative colitis	Maxil. hypoplasia Prognathism High. alkaline phosphatase OFC 98% Normal glycerol excretion		

*+, present; −, absent; blank, no data.
[a]Omitted because meaningful measurement and/or determination cannot be made because of kyphoscoliosis, clubfoot, etc.
[b]Normal phosphokinase was 86 IU/l (normal range, 37–306 IU/l).
[c]Lip disparity: relatively thin upper lip and full lower lip.

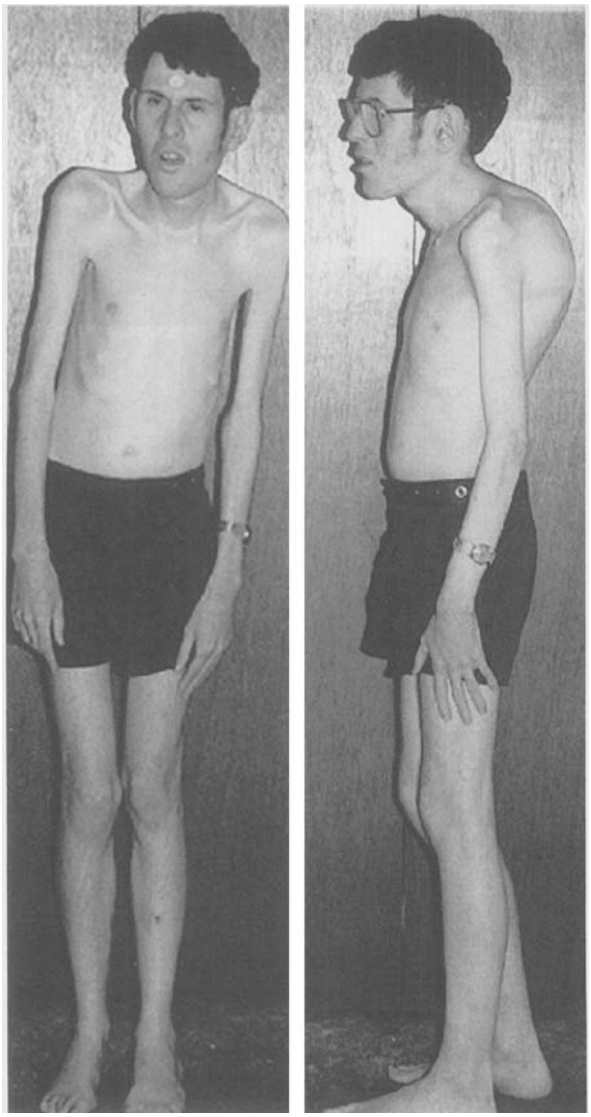

Fig. 2. Physical appearance of patient III-10. Note thin build, minimal musculature, and kyphoscoliosis. He was the index case in Snyder and Robinson [1969].

Fig. 3. Appearance of affected males in childhood and as adults, arranged by pedigree number. Top to bottom: III-1 (ages 4 and 41), III-6 (ages 5 and 32), III-8 (ages 8 and 28), III-9 (ages 5 and 19), and III-10 (ages 6 and 27). Note change from a normal appearance more than 20 years ago to an abnormal adult facial appearance which was distinctly different from unaffected sib. All affected adults have a slightly prominent lower lip, with relatively thin upper lip, and 4/5 have slight facial asymmetry. In Snyder and Robinson [1969], only III-10 (at age 3 and as shown above at age 6) and III-1 (at age 16) were noted to have facial asymmetry. All other affected males were reported as having normal facies.

delivery. His birth weight was 3,180 g. At 17 months he was not walking or talking. He was in special education and received speech therapy. His IQ was reported as 60. At age 20 he was found to have osteoporosis. This was detected on X-ray examination following a sledding accident which resulted in multiple thoracic vertebral compression fractures. He lives in an institution and performs janitorial work.

His face is somewhat coarse with a large mouth and full lower lips with facial asymmetry (Fig. 3). Palate is normal. He also is tall with an asthenic build, with moderately diminished muscle bulk and kyphoscoliosis. His strength is normal. He has long hands (Table I) and mildly hyperextensible fingers and long great toes (Fig. 4). He is oriented to person, place, and time; however, he was somewhat suspicious during interview, and laughed inappropriately at times. His speech is thick and slow. He can follow commands and repeat names, but has poor performance on simple calculations. His neurologic examination was normal. A recent MRI was normal.

Patient IV-2. Patient IV-2 died at age 2 weeks in 1976. He was noted to have a bifid uvula and high-arched palate at birth. He never fed well and never regained his birth weight prior to his death. Autopsy showed a small ventricular septal defect (VSD) and patent atrial septal defect, with slightly enlarged heart

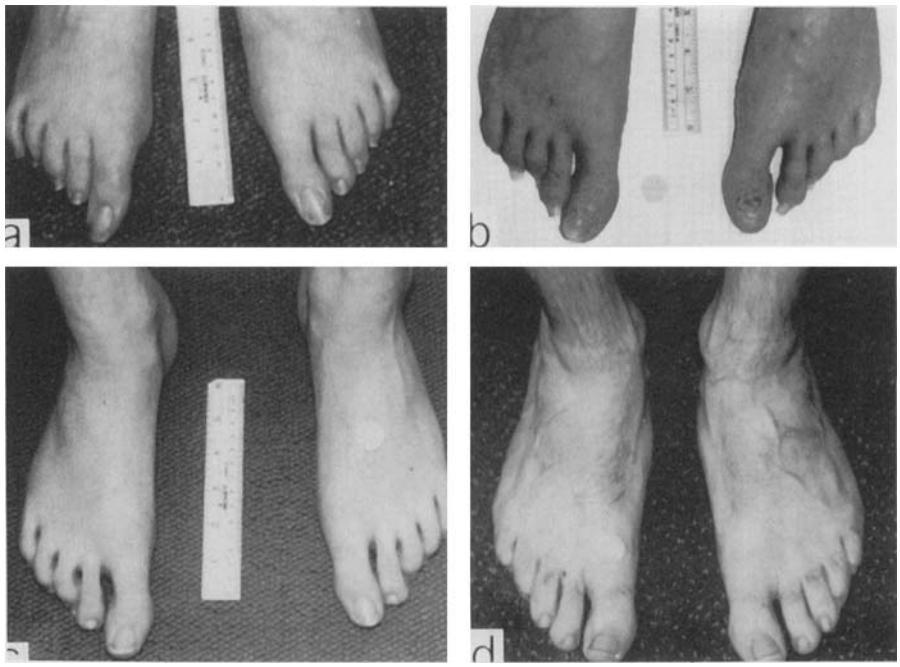

Fig. 4. Appearance of feet in patients III-6 (**a**), III-8 (**b**), III-9 (**c**), and a normal brother, III-4 (**d**). In comparison to those of the normal brother, the great toes were more than 1 cm longer than the second toe in all affected adult patients who could be measured. Although there are no norms for this measurement, the length of the great toes by appearance and measurement were different from those of normal siblings.

size and acute pneumonitis. Autopsy of his brain was normal. One adrenal gland showed intact cortical and medullary cells. The other showed extensive calcification of the cortical region of the adrenal gland, with less involvement of the medulla. At autopsy, it was felt that his death was secondary to several factors which included acute, massive pneumonitis of probable viral origin, a high ventricular septal defect in the heart, and possibly an inadequate adrenal steroid response, since one adrenal gland was almost totally calcified.

Patient IV-4. Patient IV-4, a 2-year-old boy, was born after a 32-week gestation with intrauterine growth retardation. He weighed 1,860 g and was delivered by cesarean section. Development has always been delayed. He sat at about 1 year, pulled himself up at 16 months, and now takes a few steps with support. His head size has always been at the 50th centile, although statural growth has been less. He has occasional involuntary brief jerks. His forehead is prominent. Facies are symmetrical while resting, but while crying the left side of the mouth droops (Fig. 5). Testes were not palpated and the scrotum appeared minimally rugose. He has puffy, thick feet, with hammer, toes bilaterally. His overall tone was decreased. A quick jerk of his limbs every 10–20 seconds occurred during the examination. None of the physical traits found in adults (Table I) were observed.

Special Studies

Cytogenetic studies. High-resolution chromsome analyses and fragile-X analyses were performed on II-2, II-3, III-3, III-10, and IV-4, and were normal.

MRI evaluation. An MRI examination of the brain was normal in patients III-8 and III-9.

Molecular Studies

Molecular and linkage analysis. Initial studies indicated linkage to the marker DXS84 near the DMD locus in Xp21.2 [Arena et al., 1992; Schwartz et al., 1992]. Further analysis focused on this region, using polymorphisms within and distal to the dystrophin gene (Table II). The dystrophin markers detected recombination within the dystrophin gene and at either end of the gene, making it unlikely that the DMD locus was involved in Snyder-Robinson syndrome. Furthermore, PCR analysis of peripheral lymphocyte DNA from 3 affected individuals showed no apparent deletions of either glial-specific brain promoter or muscle-specific promoter at the 5′ end of dystrophin.

Haplotype analysis, presented in Figure 6, demonstrated informative crossovers in 2 unaffected males (II-5 and II-6) and 1 affected male (III-9). The crossovers define the limits of the SRS gene region to be DXS43 (distal) and 3′ DMD (proximal). An eight-locus analysis was conducted using the following order and genetic distances: DXS987–3 cM–DXS43–5 cM–DXS443–5 cM–DXS41–3 cM–DXS989–3 cM–DXS28–3 cM–3′ Dys [Gyapay et al., 1994; Willard et al., 1994]. Multipoint analysis gave a maximum lod score of 4.7 with DXS989. The multipoint curve had lod-1 confidence limits which defined a 15-cM region extending from 3 cM distal to DXS443 to 4 cM proximal to DXS989. This region would thus be flanked by DXS43

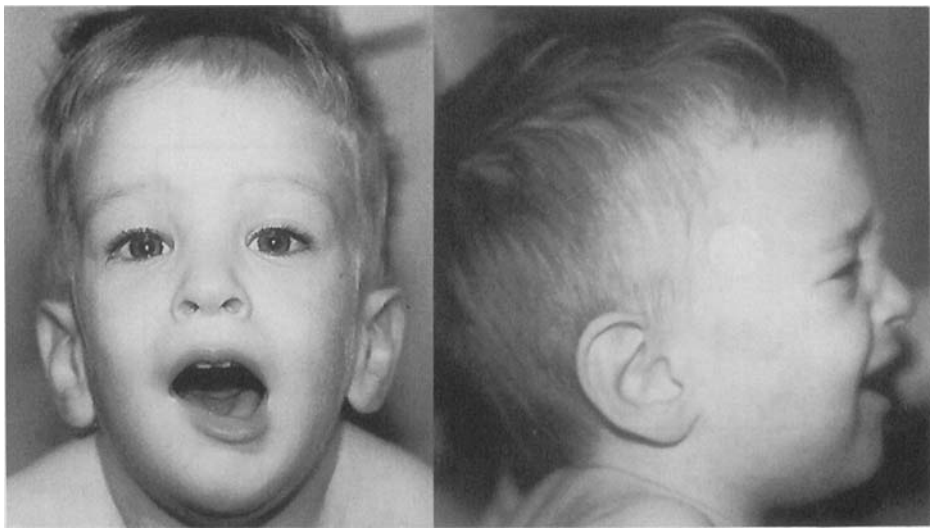

Fig. 5. Patient IV-4. Note asymmetrical lower face when crying.

(distal) and 3′ dystrophic immuno fluorescence (DMD) (proximal), which is in agreement with the haplotype analysis.

Molecular studies: Muscle biopsy. Biopsy showed nearly normal muscle histology. There were a few isolated atrophic fibers, which may be found in normal muscle. By five dystrophin immunofluorescence antibodies, all fibers were dystrophin-positive, with strong peripheral labeling. A normal control muscle biopsy was run in parallel for all antibodies, and the results were indistinguishable from patient's muscle. Within the limits of these studies, which included about 70% of the dystrophin protein [Hoffman et al., 1987, 1990], there was no detectable dystrophin protein abnormality.

DISCUSSION

In the original report of this family by Snyder and Robinson in 1969, the retarded males were described as having nothing unusual or characteristic about their facies or habitus. Two, however, had facial asymmetry, with slight flattening of the face in III-10 (current pedigree) and slight asymmetry in III-1. Titubation (III-10) and nonspecific neurologic findings, such as a wide-based, unsteady gait (III-10) or a hypotonic clumsy, wide-based, disequilibrated gait were described. "Retardation, hypotonia, and disequilibration" were indicated as characteristic of the affected individuals. They ranged from age 4–18 years. Thus, most of the current findings must have developed since that time

TABLE II. Results of Pairwise Linkage Analysis of X Chromosome Markers

		Recombination fractions (θ)							
Locus	Location	0.001	0.01	0.05	0.10	0.20	0.30	Θ_{max}	Z_{max}
DXS16	Xp22.31	0.29	0.29	0.27	0.25	0.20	0.14	0.00	0.29
DXS987	Xp22.31	−1.48	0.46	1.59	1.84	1.70	1.26	0.12	1.86
DXS43	Xp22.2	0.21	1.14	1.55	1.48	0.99	0.30	0.06	1.56
DXS443	Xp22.13	3.26	3.21	3.02	2.76	2.20	1.57	0.00	3.26
DXS41	Xp22.13	3.20	3.16	2.94	2.67	2.09	1.46	0.00	3.20
DXS989	Xp22.13	4.21	4.14	3.86	3.48	2.66	1.74	0.00	4.21
DXS28	Xp22.11	3.39	3.33	3.13	2.86	2.29	1.64	0.00	3.39
DMD 3′	Xp21.2	0.91	1.85	2.30	2.28	1.88	1.30	0.07	2.32
Str45	Xp21.2	1.51	2.45	2.88	2.83	2.39	1.74	0.07	2.89
Str49	Xp21.2	1.51	2.45	2.88	2.83	2.39	1.74	0.07	2.89
DXS164	Xp21.2	3.26	3.21	3.02	2.76	2.20	1.57	0.00	3.26
DMD 5′	Xp21.2	1.21	2.15	2.58	2.54	2.11	1.51	0.06	2.32
DXS84	Xp21.1	0.37	1.31	1.76	1.74	1.35	0.79	0.07	1.78
DXS7	Xp11.3	0.06	0.06	0.06	0.05	0.04	0.03	0.00	0.06
DXS255	Xp11.23	−10.17	−6.89	−3.21	−1.64	−0.35	0.13	0.38	0.22
DXS106	Xq12	−3.36	−1.71	−0.51	−0.16	−0.07	−0.21	0.50	0.27
TCD	Xq21.2	−6.38	−3.41	−1.43	−0.68	−0.01	0.08	0.35	0.10
DXS144E	Xq26	−5.73	−2.77	−0.82	−0.10	0.40	0.47	0.28	0.48
DXS548	Xq27.3	−12.8	−7.51	−3.53	−1.98	−0.71	−0.20	0.45	0.02
DXS52	Xq28	−10.5	−7.50	−4.70	−2.87	−1.19	−0.44	0.50	0.00

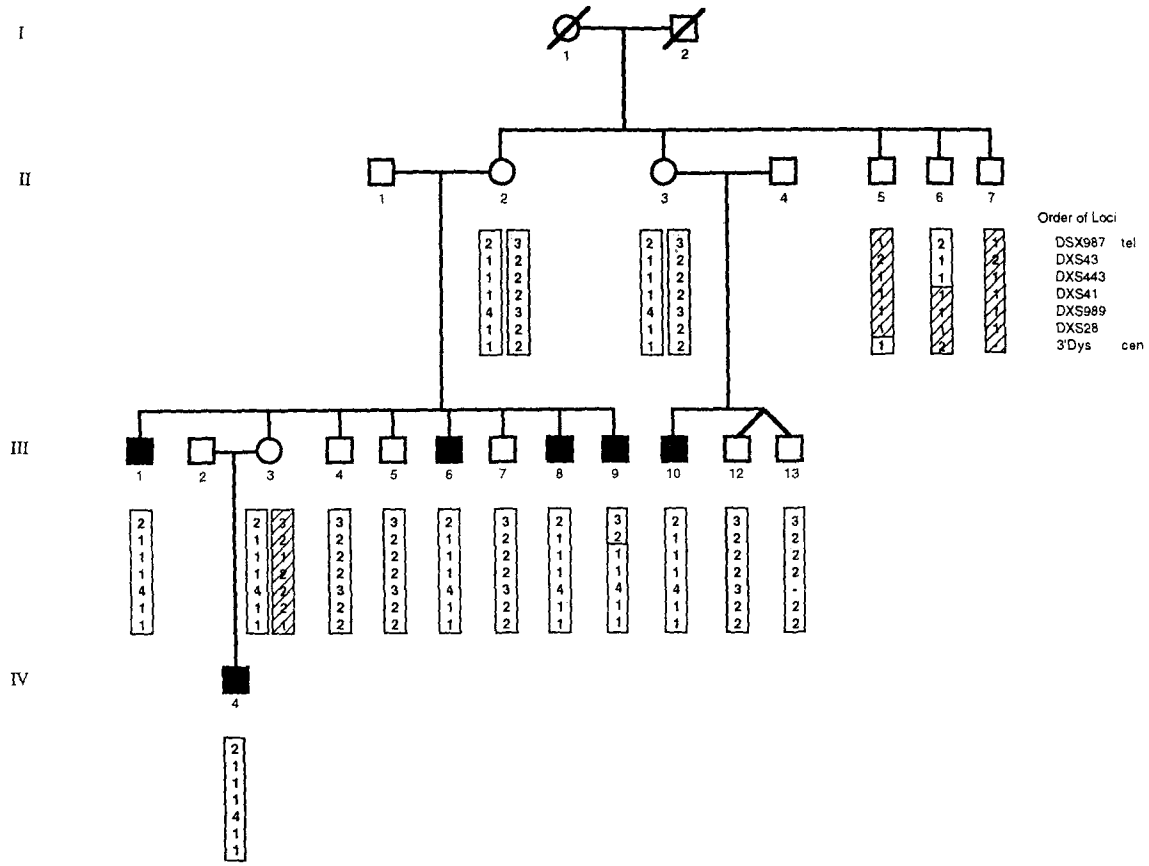

Fig. 6. Partial pedigree of family K8145, showing the haplotype of markers linked to the SRS gene. Haplotype segregating with the syndrome is indicated by open rectangles.

or have been sufficiently mild that they did not raise the question of other consistent findings. The criteria for diagnosis of this disorder in XLMR families, therefore, depend upon the age of an affected male, since many findings were not present at a young age in the one young affected family member examined by us, in the original report, or in photographs provided by the family.

The current findings in affected adults (Table I) include a thin habitus with minimal musculature (5/5), significant kyphoscoliosis (4/5) with osteoporosis (4/4) and multiple fractures (3/5), long hands (5/5) and great toes (3/3), and hyperextensible fingers (4/5), together with facial asymmetry of the lower face or about the eyes (4/5) and a relatively full lower lip and small upper lip (5/5) (Fig. 3). Neurologic findings remained nonspecific and variable.

The reason for the osteoporosis and multiple fractures (III-1 and III-6 and III-8, Table I) remains unclear. In one individual (III-1), the fractures were sufficiently severe and unexplained as to raise the question of osteogenesis imperfecta on several occasions, but the diagnosis was never substantiated. Routine laboratory tests were normal. Presumably, the multiple fractures played a significant role in the present wheelchair-bound status of III-1. Height in those with the most severe kyphoscoliosis (III-6 and III-10) could not be evaluated adequately, but in III-8 and III-9, both of whom also had significant but lesser kyphoscoliosis, the height was still at or above the 95th centile. Thus, it is possible that at some point nearly all were tall or very likely would have been tall without the intervening kyphoscoliosis. In 4 of 5 affected males, weight was at or below the 5th centile. Long hands (≥95th centile) were present in all adults who could be evaluated. The great toes in the 3 affected males who could be evaluated were unusually long (Fig. 4a–c). In III-4 (Fig. 4d) and other normal males this was not observed. This may be a useful physical finding in suggesting the diagnosis of Snyder-Robinson syndrome in other XLMR families with an unknown diagnosis, at least in older males.

Asymmetry about the eyes, shown in Figure 3, with or without slight lower face asymmetry in retarded males, should also suggest this diagnosis. Asymmetry of the orbital regions was not present in early childhood, either in the photographs in Snyder and Robinson [1969] or in other photographs supplied by the family. Thus, it likely developed during the teens or early twenties. However, lower facial asymmetry was present in early childhood in 2, and may also be a helpful early diagnostic sign. In the youngest affected male examined (IV-4) left facial asymmetry was clearly pres-

ent, but only when crying (Fig. 5). The relative fullness of the lower lip with a small upper lip was present in IV-2 at age 2 and may also have been present in others, as shown by their childhood photographs (Fig. 3). Either of these findings may be helpful in suggesting an early diagnosis of Snyder-Robinson syndrome (SRS).

Nasal or dysarthric speech was present in all and was associated with a high narrow or cleft palate (III-6 and III-9). Neurologic disability (spastic paraplegia) was most severe in III-1, but was characterized only by less severe and nonspecific findings in others, as described in Table I.

One affected relative (III-1) displayed progressive neurologic findings, but there was no evidence of cerebellar abnormalities or spasticity in others, and MRI scans in 2 affected males were normal. Increased testicular size or other organ involvement was not noted. There was no suggestion of involvement in carrier females or anticipation.

Thin habitus with decreased muscle mass also occurs in Lujan syndrome (MIM 309520), at least during adolescence, and Allan-Herndon-Dudley (AHDS) syndrome (MIM 309600). Both the present family and the original family reported with Lujan syndrome [Lujan et al., 1984] also have high narrow palates and a hypernasal voice, as well as kyphoscoliosis in some relatives. However, the Lujan family did not have a prominent great toe, full lower lip, cleft palate, osteoporosis, or fractures. Moreover, a preliminary linkage analysis of the original Lujan family using markers DXS989 and DXS987 detected at least one recombination for each marker [Lubs, unpublished data]. These results, as well as the clinical differences, make it unlikely that SRS and Lujan syndrome are allelic, but one cannot absolutely rule out the possibility. The absence of cerebellar and other clear or localizing neurologic signs distinguishes this syndrome from AHDS and others where ataxia or spastic paraplegia are initially evident or become evident with time. The localization also differs from that of AHDS (Xq21). The SRS locus is distinct from the Duchenne locus, so that muscle hypoplasia can currently only be interpreted as a recurring finding in XLMR syndromes which is unexplained, and not due to a decrease or abnormality of dystrophin.

A number of mapped disorders with XLMR overlap the localization in this family. Several, such as Coffin-Lowry (MIM 303600), Rud (MIM 308200), MIDAS (MIM 309801), Aicardi (MIM 304050), and Nance-Horan (MIM 302380) syndromes are not likely to be due to the same gene because of clear clinical differences. Although one family with X-linked Charcot-Marie-Tooth syndrome (MIM 302801) has been reported with mental retardation, there was no evidence of peripheral neuropathy in the present family.

However, several disorders in this region warrant special comment. Patients with glycerol kinase deficiency (MIM 307030) also have osteoporosis and fractures, but glycerol excretion in patient III-9 was normal. Although one male in this family may have died of adrenal insufficiency, autopsy showed only one abnormal adrenal gland, which was calcified, and no other affected males have shown any clinical evidence of adrenal insufficiency. Because of his early death, it is not clear whether this relative was affected or normal (Table I). Thus, congenital adrenal hypoplasia (MIM 300200), which maps to this region, is also not likely to be due to the same mutation. The family with mental retardation and dystonic movements of the hand previously reported by Partington et al [1988] (MIM 309510) was restudied by Gedeon et al. [1994] with localization to a region between 3′ DXS365 and DXS28, which also overlaps with this region. Although one member of the Partington family showed scoliosis, no dystonia was noted in the present family.

Fourteen families with nonspecific XLMR also localize to this region: MRX 2,9,10,11,12,13,15,19,21,29,32, 33,37,38 [Lubs et al 1996a; Gedeon et al., 1996]. It is possible that the present family and any or all of these 14 families could be due to mutations at the same locus, but none had similar clinical findings and/or a similar location of their maximum lod score. Although the present report of the Snyder-Robinson family describes it as a syndrome, it was originally termed nonspecific XLMR, and the syndrome has only become apparent over time.

Overall, these results suggest that this family represents a unique syndrome manifested by mental retardation, thin habitus with decreased muscle mass, osteoporosis and multiple fractures, kyphoscoliosis, nasal speech, high narrow or cleft palate with prominent lower lips, slight but progressive facial asymmetry over time, and long great toes. The linkage studies summarized in Table II and the subsequent multipoint analysis showed a clear localization to a region distal to the Duchenne locus of approximately 15 cM. The study illustrates the importance of both linkage studies and restudy of original XLMR families in the continuing process of understanding the many X-linked mental retardation syndromes.

ACKNOWLEDGMENTS

This work was supported by NIH Research Grant RO1HD26202. We particularly thank Eric P. Hoffman and William G. Feero for carrying out dystrophin staining and certain molecular studies, and Lisa L. Baumbach and Richard J. Bartlett for studies on dystrophin promoters. We also thank Patricia Arena for preparing the photographs and the family in the study who have graciously helped us with family photos, family history, and all tests in this study.

REFERENCES

Arena JF, Schwartz C, Stevenson RE, Lawrence L, Carpenter A, Duara R, Ledbetter D, Huang T, Lehner T, Ott J, Lubs HA (1992): Spastic paraplegia with iron deposits in the basal ganglia: A new X-linked mental retardation syndrome. Am J Med Genet 43: 471–490.

Feinberg AP, Vogelstein B (1983): A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity. Anal Biochem 132:6–13.

Gedeon A, Partington M, Mulley J (1994): X-linked mental retardation with dystonic movements of the hands (PRTS): Revisited. Am J Med Genet 51:565–568.

Gedeon AK, Glass IA, Connor JM, Mullwy JC (1996): Genetic localization of MRX27 to Xq24–26 defines the sixth discrete gene for nonspecific X-linked mental retardation. Am J Med Genet 64: 121–124.

Gorecki DC, Monaco AP, Derry JM, Walker AP, Barnard EA, Barnard PJ (1992): Expression of four alternate dystrophin transcripts in brain regions regulated by different promoters. Hum Mol Genet 1:505–510.

Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, Bernardi G, Lathrop M, Weissenbach J (1994): The 1993–94 Genethon human genetic linkage map. Nat Genet Suppl 7:246–249.

Hoffman EP, Brown RH, Kunkel LM (1987): Dystrophin: The protein product of the Duchenne muscular dystrophy locus. Cell 51: 919–928.

Hoffman EP, Moran JE, Watkins SC, Slayter HS, Partridge TA (1990): Somatic revision/suppression of the mouse mdx phenotype in vivo. J Neurol Sci 99:9–25.

Klamutt HJ, Gangopadhyay SB, Worton RG, Ray PN (1990): Molecular and functional analysis of the muscle-specific promoter region of the Duchenne muscular dystrophy gene. Mol Cell Biol 10: 193–205.

Lathrop GM, Lalouel JM (1984): Easy calculations of lod scores and genetic risks on small computers. Am J Hum Genet 36:460–465.

Lathtrop GM, Lalouel JM, Julier C, Ott J (1985): Multilocus linkage analysis in humans: Detections of linkage and estimation of recombination. Am J Hum Genet 37:482–498.

Lubs HA, Chiurazzi J, Arena JF, Schwartz C, Tranebjaerg L, Neri G (1996a): XLMR genes: Updated 1996. Am J Med Genet 64:147–157.

Lubs HA, Schwartz CE, Stevenson RE, Arena JF (1996b): Study of X-linked mental retardation (XLMR): Summary of 61 families in the Miami/Greenwood study. Am J Med Genet 64:169–175.

Lujan JE, Carlin ME, Lubs HA (1984): A form of X-linked mental retardation with marfanoid habitus. Am J Med Genet 17:311–322.

Makover A, Zuk D, Breakstone J, Yaffe D, Nudel U (1991): Brain-type and muscle-type promoters of the dystrophin gene differ greatly in structure. Neuromusc Disord 1:39–45.

Parington MW, Mulley JC, Sutherland GR, Hockey A, Thode A, Turner G (1988): X-Linked mental retardation with dystonic movements of the hands. Am J Med Genet 30:251–262.

Rapaport D, Fuchs O, Nudel U, Yaffe D (1992): Expression of the Duchenne muscular dystrophy gene products in embryonic stem cells and their differentiated derivatives. J Biol Chem 267: 21289–21292.

Schwartz CE, Ulmer J, Brown A, Panscot I, Goodman HO, Stevenson RE (1990): Allan-Herndon syndrome II. Linkage to DNA markers in Xq21. Am J Hum Genet 47:454–458.

Schwartz LS, Tarleton J, Popovich B, Seltzer W, Hoffman EP (1992): Fluorescent multiples linkage analysis and carrier detection for Duchenne/Becker muscular dystrophy. Am J Hum Genet 51: 721–729.

Snyder RD, Robinson A (1969): Recessive sex-linked mental retardation in the absence of other recognizable abnormalities: Report of a family. Clin Pediatr (Phila) 8:669–674.

Weissenbach J, Gyapay G, Dib C (1992): A second-generation linkage map of the human genome. Nature 359:794–801.

Willard HF, Cremers F, Mandel JL, Monaco AP, Nelson DL, Schlessinger D (1994): Report of the Fifth International Workshop on Human X Chromosome Mapping. Cytogenet Cell Genet 67: 295–358.